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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/763,933	01/23/2004	Yasuhiro Furuichi	13761 US3 (C038435/012851	8382

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EXAMINER	
FRONDA, CHRISTIAN L	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/763,933	FURUICHI ET AL.	
	Examiner	Art Unit	
	Christian L Fronda	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 January 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-16,36-39,59-62 and 82-85* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *13-16,36-39,59-62 and 82-85* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *1/23/2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/935,263.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/26/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. In the **REQUEST FOR FILING A RULE 1.53(b) DIVISIONAL APPLICATION** dated 01/23/2004, claims 1-12, 17-35, 40-58, 63-81, and 86-92 have been canceled; and the specification has been amended to cross-reference the instant application to prior US nonprovisional applications.

2. Claims 13-16, 36-39, 59-62, and 82-85 are pending and are under consideration in this Office Action.

3. The paper copy and computer readable form (CRF) of the Sequence Listing filed on 01/23/2004 have been received and have been processed by the Scientific and Technical Information Center (STIC).

4. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: Biotin synthase from Kurthia

Claim Rejections - 35 U.S.C. § 112, 2nd Paragraph

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 13-16, 36-39, 59-62, 82-85 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In each of claims 13, 36, 59, and 82, the phrase "functional derivatives thereof" renders each of the claims vague and indefinite because it is unclear as what specific biological function or enzymatic activity is possessed by the recited "derivatives thereof". Although the specification states that the "functional derivatives" have amino acid sequences that have addition, insertion, deletion, and/or substitution of one or more amino acid residues, the claims do not recite the specific biological function or enzymatic activity possessed by the recited

"derivatives thereof".

Furthermore, it is not clear whether applicants actually intended that the claims recite "...a polynucleotide which encodes the polypeptide of SEQ ID NO: 8 **or** functional derivatives thereof" (emphasis added).

Claims 14-16 which depend from claim 13 are also rejected because they do not correct the defect of claim 13. Claims 37-39 which depend from claim 36 are also rejected because they do not correct the defect of claim 36. Claims 60-62 which depend from claim 59 are also rejected because they do not correct the defect of claim 59. Claims 83-85 which depend from claim 82 are also rejected because they do not correct the defect of claim 82.

For examination purposes, the claims are assumed to recite an isolated DNA molecule which comprises a polynucleotide which encodes the polypeptide of SEQ ID NO: 8 **or** functional derivatives thereof.

In each of claims 14, 37, 60, and 83, part "b)" of each of the claims renders the claims vague and indefinite because the specific amino acid sequence of the biotin synthase which is to be encoded by the recited polynucleotide of part a) is not known and not recited.

Amending the claim to recite a "polynucleotide encoding the polypeptide of SEQ ID NO: 8" may overcome the rejection.

In each of claims 14, 37, 60, and 83, part "c)" of each of the claims renders the claims vague and indefinite because the specific "stringent hybridization conditions" are not known, not recited, and not specifically defined by the specification. Although the specification on p. 7, lines 29-35, describe a variety of conditions which are intended to be standard conditions for hybridization or stringent hybridization conditions, there is nothing to suggest that other conditions would not also be included within the scope of "stringent hybridization conditions". In the art, what is considered stringent hybridization varies widely depending on the individual situation as well as the person making the determination. As such it is unclear how homologous to the sequence of SEQ ID NO: 7 a polynucleotide must be to be included within the scope of the claim.

The claims should be amended to recite the specific "stringent hybridizing conditions" (e.g., hybridization buffer composition and hybridization temperature) in order to define the metes and bounds of the stringent hybridization wash conditions.

In each of claims 15, 38, 61, and 84, part "b)" of each of the claims renders the claims vague and indefinite because the specific amino acid sequence of the biotin synthase which is to be encoded by the recited polynucleotide of part a) is not known and not recited.

Amending the claims to recite a "polynucleotide encoding the polypeptide of SEQ ID NO: 8" may overcome the rejection.

Claim Rejections - 35 U.S.C. § 112, 1st Paragraph

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 13, 36, 59, and 82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

For examination purposes as stated above, each of claims 13, 36, 59, and 82 is assumed to recite an isolated DNA molecule which comprises a polynucleotide which encodes the polypeptide of SEQ ID NO: 8 **or** functional derivatives thereof.

Claims 13, 36, 59, and 82 are a genus claims that is directed toward any DNA molecule comprising any polynucleotide encoding a polypeptide of SEQ ID NO: 8 or any functional derivative of a polypeptide of SEQ ID NO: 8, where the said functional derivative is any polypeptide of any amino acid sequence, structure, and biological function which can be made or derived from the polypeptide of SEQ ID NO: 8, and where the amino acid sequence of the derivative has amino acid insertions, deletions, substitutions, and combinations thereof in SEQ ID NO: 8 as defined by the specification (see p. 7, lines 5-8).

Thus, the scope of the claims includes many polynucleotides encoding polypeptides with widely differing structural, chemical, and physical characteristics and widely differing biological functions. Furthermore, the genus is highly variable because a significant number of structural differences between genus members is permitted, genus members have different biological functions, and genus members are from many biological sources.

The specification discloses a *Kurthia* sp. biotin synthase consisting of the amino acid sequence of SEQ ID NO: 8 which is encoded by the polynucleotide of SEQ ID NO: 7. However, neither the specification nor the general knowledge of those skilled in the art provide evidence of any description of a structure which would be expected to be common to the members of the genus and would distinguish members of the genus from other polynucleotides. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed.

The disclosed polynucleotide of SEQ ID NO: 7 encoding the biotin synthase of SEQ ID NO: 8 is not representative of the claimed genus since other members of the genus have widely differing amino acid sequences, structures, and biological functions. The specification fails to

provide a written description of representative polynucleotides encoding polypeptides as encompassed by the claimed genus. Furthermore, there is no recitation of any particular structure to function/activity relationship in claims 13, 36, 59, and 82 that clarify what common biological function is shared by members of the claimed genus.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, the disclosed polynucleotide of SEQ ID NO: 7 encoding the biotin synthase of SEQ ID NO: 8 alone is insufficient to describe the genus. In view of the above considerations, one of skill in the art would conclude that Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed DNA molecule comprising any polynucleotide encoding any functional derivative of a polypeptide of SEQ ID NO: 8.

9. Claims 13, 14, 36, 37, 59, 60, 82, and 83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated DNA molecule comprising a polynucleotide which encodes the polypeptide of SEQ ID NO: 8; does not reasonably provide enablement for any other embodiment. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of claims 13, 36, 59, and 82 encompass any DNA molecule comprising any polynucleotide encoding a polypeptide of SEQ ID NO: 8 or any functional derivative of a polypeptide of SEQ ID NO: 8, where the said functional derivative is any polypeptide of any amino acid sequence, structure, and biological function which can be made or derived from the polypeptide of SEQ ID NO: 8, and where the amino acid sequence of the derivative has amino acid insertions, deletions, substitutions, and combinations thereof in SEQ ID NO: 8 as defined by the specification (see p. 7, lines 5-8). SEQ ID NO: 8 is disclosed as consisting of 338 amino acid residues.

The nature and breadth of claims 14, 37, 60, and 83 encompass any DNA molecule comprising any polynucleotide encoding a biotin synthase, where the said any polynucleotide encoding a biotin synthase hybridizes under any stringent hybridization conditions to SEQ ID NO: 7.

In order to meet the enablement requirement, one skilled in the art must be able to make and/or use the invention of claims 13, 14, 36, 37, 59, 60, 82, and 83 without undue experimentation using the specification coupled with information known in the art. However, neither the specification nor the general knowledge of those skilled in the art provide guidance or prediction on making, without undue experimentation, the polynucleotides encoding the functional derivatives of claims 13, 36, 59, and 82 and the polynucleotides of claims 14, 37, 60, and 83 that hybridize under any stringent hybridization conditions to SEQ ID NO: 7.

Although the specification discloses a *Kurthia* sp. biotin synthase consisting of the amino acid sequence of SEQ ID NO: 8 which is encoded by the polynucleotide of SEQ ID NO: 7, the specification, however, does not provide guidance or prediction regarding the specific structural and catalytic amino acids residues in SEQ ID NO: 8 that are essential for enzyme activity which cannot be altered. Nor does the specification provide guidance or prediction regarding the specific amino acid residues within the full length polypeptide of SEQ ID NO: 8 that can be changed without destabilizing protein structure and inactivating enzyme activity. Furthermore, the specification does not provide working examples on selecting any specific amino acid residues to change which does not result in loss of biotin synthase activity of the disclosed polypeptide of SEQ ID NO: 8.

The general knowledge of those skilled in the art does not provide any guidance or prediction regarding the specific structural and catalytic amino acids residues in SEQ ID NO: 8 which cannot be altered, and specific amino acid residues in SEQ ID NO: 7 that can be changed without destabilizing protein structure and inactivating enzyme activity. The prior art as exemplified by Broun et al. (Science. 1998 Nov 13;282(5392):1315-7) teach that minor modifications to a protein sequence can completely alter the function of a protein. Broun et al. show that as few as four amino acid substitutions in a polypeptide consisting of 380 amino acid residues changes the enzymatic activity of the polypeptide from a desaturase to a hydroxylase (seen entire publication, especially the abstract and pp. 1316-1317).

Since neither the specification nor information known in the art provide guidance or prediction for the specific amino acid residues that can be changed without inactivating enzyme activity, one must perform an enormous amount of trial and error experimentation to determine which amino acid residues in SEQ ID NO: 8 can be changed to make a polypeptide that is functional derivative of a polypeptide of SEQ ID NO: 8, where the amino acid sequence of the derivative has amino acid insertions, deletions, substitutions, and combinations thereof in SEQ ID NO: 8; and yet has biotin synthase activity in order to meet the limitations of claims 13, 36, 59, and 82.

Such trial and error experimentation is well outside the realm of routine experimentation and entails selecting any amino acid residues in SEQ ID NO: 8 to modify, searching and screening for the type of modification to perform on the selected amino acid residues (deletion, insertion, substitution, additions or combinations thereof) which will not result in a loss of

enzyme activity, determining whether the polypeptide has any biotin synthase activity, and then making the corresponding polynucleotide encoding the polypeptide.

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the amino acid residues which can be changed without inactivating enzyme activity. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention of 13, 36, 59, and 82 is undue and well outside of routine experimentation.

Regarding the invention of claims 14, 37, 60, and 83, teachings regarding screening and searching for the claimed invention using enzyme assays and varying any hybridization conditions stated in the specification is not guidance for making any polynucleotide that hybridize under any stringent hybridization conditions to SEQ ID NO: 7 and encodes any biotin synthase. The general knowledge of those skilled in the art does not provide any guidance or prediction regarding any stringent hybridization conditions which can be used to determine and identify any polynucleotide that can hybridize to SEQ ID NO: 7 and encode any biotin synthase.

Since neither the specification nor information known in the art provide guidance or prediction for the specific hybridization conditions, one must perform an enormous amount of trial and error experimentation to determine the hybridization conditions which will facilitate any polynucleotide of any nucleotide sequence to hybridize to SEQ ID NO: 7, where the hybridized polynucleotide must encode any biotin synthase.

Such trial and error experimentation is well outside the realm of routine experimentation and entails searching and screening for any polynucleotide of any nucleotide sequence in any biological source which will hybridize under any stringent hybridization condition and then determining whether the polynucleotide encodes a functional biotin synthase by recombinantly expressing the polynucleotide .

The Examiner finds that one skilled in the art would require additional guidance, such as information regarding the specific stringent hybridization conditions, e.g. buffer composition and temperature. Without such a guidance, the amount of experimentation left to those skilled in the art to make the invention of 14, 37, 60, and 83 is undue and well outside of routine experimentation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 13, 14, 36, 37, 59, 60, 82, and 83 are rejected under 35 U.S.C. 102(b) as being anticipated by Ohsawa et al. (Gene. 1989 Aug 1;80(1):39-48; and Accession M27867).

Ohsawa et al. teach the following:
(1) an isolated 8.2kb DNA molecule comprising a 996 bp polynucleotide (see Accession M27867) that encodes a biotin synthase (also known as biotin synthetase) (see entire publication, especially p. 41, right column, **(a) Cloning of the *Bacillus sphaericus bioB gene*** and **(b) Nucleotide sequence of the *Bacillus sphaericus* T-178-367 *bioB* gene**), which is expected to hybridize to SEQ ID NO:7 since no specific hybridization conditions have been recited and an alignment between Accession M27867 shows nucleotide regions of Accession M27867 that are identical to SEQ ID NO: 7 where hybridization can occur because of complementary base-pairing (seen enclosed nucleotide alignment);

(2) a plasmid expression vector containing said polynucleotide (Accession M2786) encoding a biotin synthase (see p. 42, right column **(c) Construction of an *Escherichia coli bioB* expression vector and evaluation of biotin production in transformed cells**; p. 44, Fig. 3); and

(3) an *Escherichia coli bioB* strain expressing biotin is transformed with said plasmid expression vector and a process for the production of biotin by culturing an *E.coli* cells or *Bacilli* cells transformed with said vector and isolating the produced biotin from the culture medium, where the culture medium is centrifuged and biotin amounts measured in the supernate (see p. 41, left column, **(e) Growth conditions and bioassay of biotin**; p. 42, right column **(c) Construction of an *Escherichia coli bioB* expression vector and evaluation of biotin production in transformed cells**; and p. 44, left column, **(d) Expression of the *bioB* gene and biotin production in bacilli**). It is known in the prior art that *Escherichia coli* produces and expresses biotin (see Sanyal et al. Arch Biochem Biophys. 1996 Feb 1;326(1):48-56.). Thus, the transformed *E.coli* strains that are transformed have the ability to produce and express biotin prior to transformation with the said plasmid expression vector.

Because the 996 bp polynucleotide (Accession M27867) encoding biotin synthase taught by Ohsawa et al. is expected to hybridize to SEQ ID NO: 7, the teachings of Ohsawa et al. stated above anticipate the invention of claims 14, 37, 60, and 83.

Because the 996 bp polynucleotide (Accession M27867) encoding a biotin synthase having has an nucleotide identity of 37.6% to SEQ ID NO: 7, the said 996 bp polynucleotide

(Accession M27867) encodes a functional derivative of the polypeptide of SEQ ID NO: 8 since the encoded biotin synthase of Ohsawa et al. has an amino acid sequence that has amino acid insertions, deletions, substitutions, and combinations thereof in SEQ ID NO: 8 (see attached amino acid alignment). Thus, the said polynucleotide (Accession M27867) falls within the scope of the claimed polynucleotide which encodes "functional derivatives" of the polypeptide of SEQ ID NO:8 as defined by the specification, and the teachings of Ohsawa et al. stated above anticipate the invention of claims 13, 36, 59, and 82.

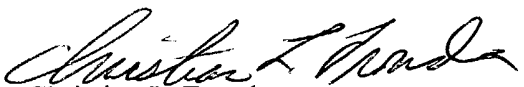
Conclusion

12. No claim is allowed.

13. An isolated polynucleotide encoding a biotin synthase having an amino acid sequence of SEQ ID NO: 8, and an isolated polynucleotide of SEQ ID NO: 7 are free of the prior art

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christian L Fronda whose telephone number is (571)272-0929. The examiner can normally be reached Monday-Friday between 9:00AM - 5:00PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura N Achutamurthy can be reached on (571)272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

15. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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